Abstract

Objective: Adrenocortical carcinoma (ACC) is a rare malignancy with a poor prognosis. Herein, we describe the clinical features and outcomes for a large series of ACC patients.

Design and methods: Retrospective review of ACC patients seen at The University of Texas MD Anderson Cancer Center from 1998 through 2011.

Results: A total of 330 patients with median age at diagnosis of 48.5 years: 12 (3.6%) patients were under 18 years. Hormonally functioning tumors represented 41.8% (n = 138) of all cases. Surgical resection for the primary tumor was done in 275 (83.3%) patients (45 at MD Anderson (16.4%)). For those who had surgical resection, the median local-recurrence-free time was 1.04 years. Factors associated with local recurrence included positive surgical margins (P = 0.007) and advanced disease stage (P = 0.026). Median overall survival time for all patients was 3.21 years. Median survival times were 24.1, 6.08, 3.47, and 0.89 years for stages I, II, III, and IV respectively. In multivariable analysis, older age, functioning tumors, and higher disease stage remained significant prognostic factors associated with poor survival.

Conclusion: ACC prognosis remains poor with the use of currently available treatments. Older age, functioning tumors, and incomplete resections are clinical factors associated with poor survival. Surgical expertise is important to achieve complete resections and to improve outcome.


Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy with an estimated annual incidence of about two cases per million people (1, 2, 3). Most of our knowledge about ACC is derived from case series that reflected national databases and tertiary referral centers’ experience (4, 5, 6, 7, 8).

As the first case series of malignant suprarenal tumors was described by Ramsay in 1899 (9), many milestones have been reached in the treatment and management of ACC, including the discovery of cortisone in the 1940s (10) and the introduction of mitotane in the 1960s (11). In the past few decades, better characterization of the molecular alterations that may occur in these tumors (TP53 mutation found in Li–Fraumeni syndrome (12), the APC and CTNNB1 genes in familial adenomatous polyposis coli (13, 14), and the CDKN1C (15) and IGF2 (16, 17) genes associated with Beckwith–Wiedemann syndrome) have led to the proposal of therapeutic interventions and prognostic markers in ACC (18, 19, 20). Since the publication of the last MDACC case series (5), multiple important developments have occurred, including the introduction of two staging systems (by the International Union Against Cancer in 2004 (21) and by the European Network for the Study of Adrenal Tumors (ENSAT) in 2009 (22, 23)) and the completion of the first phase III clinical trial in ACC (24).

Despite these promising developments, the estimated 5-year overall survival rate for ACC patients remains poor at 15–44% (7, 25, 26, 27). In this study, we summarize important clinical features of a large cohort of ACC patients to assess outcomes and treatment utilization in ACC over the past decade, including factors affecting prognosis. We also compared those findings with earlier reports from the same institution (4, 5, 25). Finally, we presented our current algorithms that we use to manage patients with ACC.
Subjects and methods

Patient records and study design

With the approval of the institutional review board, we retrospectively reviewed the data for ACC patients from the Tumor Registry Database of the Department of Medical Informatics at The University of Texas MD Anderson Cancer Center from 1998 through 2011. We selected 1998 as our previous series was published in 2001 and included patients from 1980 to 1997 (5).

To ensure the accuracy of this retrospective analysis, data were extracted and entered into duplicate datasets by two independent groups of investigators (S J, S E, F D, and M A H). Data fields for demographics, clinical outcomes, laboratory tests, imaging, pathologic diagnosis, and treatments were subsequently reviewed, verified, and reconciled into one database using Microsoft SQL Server version 2008 (Microsoft Corporation). It is our standard practice to confirm the diagnosis of ACC upon referral to MD Anderson for those patients who had outside surgery or biopsy before referral. The reporting of Weiss score and other markers of cell proliferation was not routinely performed and thus were not included in this report. Functional status of the tumor was determined through documentation in the medical records of cortisol, aldosterone, and/or androgen hypersecretion. Overall survival time was calculated from the date of tissue diagnosis to the date of death or to the last follow-up date. Time to local recurrence was calculated from the date of first surgical intervention. Patients who died without local recurrence were censored at the date of death. Patients were censored at the last follow-up if local recurrence or death had not occurred.

Resection margins were determined by reviewing pathology, operative reports, and perioperative records and defined as follows: R0, no evidence of tumor; R1, microscopically positive resection margins; R2, macroscopic residual disease; RX, status of resection margins is unknown.

We used the ENSAT staging classification because of its better prognostic accuracy when compared with the International Union Against Cancer staging classification for ACC (22, 23). The ENSAT staging system defines stage I as ACC measuring ≤ 5 cm in greatest dimension confined to the adrenal gland, stage II as tumor > 5 cm without extra-adrenal invasion, stage III by the presence of positive lymph nodes, infiltration of surrounding tissue, or vascular tumor extension, while stage IV includes only patients with distant metastases (22). This staging system has been in use in our institution since 1995 as proposed by Lee et al. (28) and was done at the time of operation for the 275 patients who underwent surgery and at the time of diagnosis for the 55 patients who did not have resection of the primary tumor.

We also compared patients’ characteristics and outcomes from this cohort with those reported previously from the same institution. As we did not have the original datasets for patients reported before 1998, we defined disease burden as follows: local (stage I and stage II), regional (stage III), and distant (stage IV) to facilitate comparing the results of different series.

Statistical analyses

Frequencies and percentages were reported for categorical variables. Fisher’s exact test or χ² test was used to evaluate association between two categorical variables. The Wilcoxon rank-sum test was used to evaluate the difference in the distribution of continuous variables between patient groups. The Kaplan–Meier method was used to analyze time-to-event endpoints, including overall survival and time to local recurrence. The log-rank test was used to evaluate differences in these endpoints between patient groups. Multivariable Cox proportional hazards models were fitted to include important demographic and clinical variables. All tests were two-sided. P values < 0.05 were considered statistically significant. Statistical software packages SAS 9.1.3 (SAS Institute, Cary, NC, USA) and S-Plus 8.0 (TIBCO Software, Inc., Palo Alto, CA, USA) were used for all analyses.

Results

Patients’ characteristics

Three-hundred and thirty patients with ACC were included in the current study. Most were Caucasian (n = 281, 85%) and female (n = 212, 64.2%). The median age was 48.5 years (range, 0–86 years); 12 patients (3.6%) were under the age of 18 years. ACC was associated with hormonal overproduction in 138 patients (41.8%) as follows: cortisol overproduction in 76 patients (55.1%), aldosterone overproduction in 14 patients (10.1%), androgens overproduction in 21 patients (15.2%), and overproduction of more than one hormone in 27 patients (19.6%). Median tumor size was 11 cm (range, 1–27 cm) and median tumor weight was 308 g (range, 4–3500 g). There were no cases of bilateral ACC in our cohort. Table 1 summarizes the important clinical features of this cohort and Table 2 describes patients’ characteristics and outcomes in this study compared with those reported previously from the same institution.

Associated malignancies and hereditary syndromes

Of the patients without hereditary cancer syndromes, 38 out of the 330 patients (11.5%) had other malignancies before or after diagnosis of ACC. Breast and
prostate cancers were the most common (seven patients with breast cancer (18.4%) and seven patients with prostate cancer (18.4%). Other malignancies were skin cancer (four patients, 10.5%), non-small cell lung cancer (four patients, 10.5%), endometrial carcinoma (three patients, 7.9%), papillary thyroid cancer (two patients, 5.2%), renal cell carcinoma (two patients, 5.2%), melanoma (two patients, 5.2%), bladder cancer (one patient, 2.6%), colorectal carcinoma (one patient, 2.6%), cervical cancer (one patient, 2.6%), ovarian carcinoma (one patient, 2.6%), acute lymphoblastic leukemia (one patient, 2.6%), and malignant tumors of undetermined etiology (two patients, 5.2%).

Six patients had Li–Fraumeni syndrome (diagnosed clinically or through genetic testing), one had multiple endocrine neoplasia type 1, and another patient had a familial history of ACC. No patients had Beckwith–Wiedemann syndrome or familial adenomatous polyposis.

Treatment utilization

Resection of the primary tumor was performed in 275 (83.3%) patients (n=45 (16.4%) at MD Anderson and n=230 (83.6%) outside MD Anderson). Open resection was performed in 244 (88.7%) patients and laparoscopic in 31 (11.2%) patients. Negative resection margins (R0) were achieved in 153 patients (55.6%). Positive margins (R1) were found in 47 patients (17.1%) and (R2) resection margins were found in 28 patients (10.2%). Margin status was unknown (RX) in 47 patients (17.1%).

Mitotane was used in 235 (71.2%) of the 330 patients either as monotherapy or in combination with other systemic chemotherapy. Of these, 67 (28.5%) achieved serum mitotane level of 14 mg/l or higher. The median OS for those patients with levels of 14 mg/l and higher was 4.1 years (95% CI: 2.8, 7.0 years) compared with 2.9 years (95% CI: 2.2, 3.8 years) for those who had lower mitotane levels. Figure 1 illustrates overall survival curves in both groups.

Radiation therapy was used in 58 patients (18%) mostly as a palliative measure in metastatic disease, while adjuvant radiation therapy after primary resection was used only in 16 patients (5%) (29). More than 20 different traditional chemotherapy regimens were administered as first line systemic therapy and data were available for 163 patients (Table 3).

Recurrence and survival

In patients who had surgical resection (n=275), the median local-recurrence-free time was 1.0 year (95% CI: 0.9–1.4). In univariate analysis, factors associated with local recurrence were surgical resection outside MD Anderson (P=0.035), positive surgical margins (P=0.007), and advanced disease stage (P=0.026) as shown in Table 4. On multivariate analysis, the hazard ratios for local recurrence (95% CI) including site of surgery (MDACC vs outside MDACC), stage (1/2 vs 3/4), and margin (negative vs positive) were 0.603 (0.402–0.902), 0.749 (0.533–1.053), and 0.746 (0.541–1.030) respectively. Other factors were not
associated with local recurrence and included gender, hormonal overproduction, and tumor location (right vs left).

Distant metastases were documented in 218 (66%) of the 330 patients during follow-up, with the lungs (66%), liver (57%), and bone (17%) being the most common sites.

The median overall survival time for all patients (n=330) was 3.2 years (95% CI: 2.7–4.0 years). The median follow-up time for censored observations was 2.7 years (range: 0.1–25.1 years). The median overall survival times in relation to disease stage were as follows: stage I (n=11, 3.3%), 24.1 years (95% CI: 3.2 – not reached); stage II (n=123, 37.2%), 6.1 years (95% CI: 4.9–7.2); stage III (n=111, 33.6%), 3.5 years (95% CI: 2.6–6.2); stage IV (n=85, 25.7%), 0.9 years (95% CI: 0.7–1.1). In univariable analysis, factors associated with poor survival were functioning tumors, R1/R2 surgical resections, stage III or IV at diagnosis, and venous thromboembolism (Fig. 2). Other factors such as gender and resection of five or more lymph nodes at time of initial surgery were not associated with overall survival. Older age, functioning tumors, and high disease stage at diagnosis remained significant prognostic factors associated with poor survival in a multivariable Cox proportional hazards model (Table 5).

Discussion

The current study investigates a large number of patients with ACC treated at a single institution. Compared with previous reports from our institution obtained during different time periods, patients in the current study tended to be diagnosed at an older age, have more localized tumors, and more functioning tumors. Our cohort’s 5-year survival rate of 38% is similar to those reported by others (6, 30, 31, 32), although we noticed a slightly lower 5-year survival rate than those reported from the same institution in the past. As we did not review the source documents from the older series, direct comparisons could not be done to assess if these differences are truly statistically significant. In addition, the variability in methodology may explain some of the differences in retrospectively collected data. The variation is likely small for certain outcomes (such as age, gender, date of diagnosis, death, and treatments received) but may be significant for other variables (such as performance status and certain operative complications) (33, 34, 35). In this large cohort, patients were older than patients reported in previous reports from our institution and had a higher percentage of localized disease and functioning tumors at the time of diagnosis. It remains unclear if these differences are due to increased detection of tumors at an earlier stage or a change in referral pattern. The presence of functioning tumors could lead to distinct clinical manifestations associated with excessive hormonal production and prompts further imaging studies. The theoretical benefit of earlier detection of functioning tumors is likely negated by the increased morbidity-associated hormonally active tumors compared with nonfunctioning tumors.

Surgery remains the treatment of choice for ACC (32, 36, 37), as it is the only therapeutic approach that can be curative for localized disease. In our study, complete resections of primary tumors were associated with both

### Table 4 Local-recurrence-free time of patients with adrenocortical carcinoma.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median years (95% CI)</th>
<th>Rate at 3 years (95% CI)</th>
<th>Rate at 5 years (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At MD Anderson</td>
<td>1.56 (0.82–5.52)</td>
<td>0.36 (0.24–0.55)</td>
<td>0.32 (0.2–0.52)</td>
<td>0.03</td>
</tr>
<tr>
<td>Not at MD Anderson</td>
<td>1.01 (0.83–1.37)</td>
<td>0.26 (0.21–0.33)</td>
<td>0.12 (0.08–0.18)</td>
<td></td>
</tr>
<tr>
<td>Margin status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>1.29 (1–1.79)</td>
<td>0.29 (0.23–0.38)</td>
<td>0.15 (0.1–0.23)</td>
<td>0.007</td>
</tr>
<tr>
<td>R1/R2</td>
<td>0.72 (0.42–1.03)</td>
<td>0.18 (0.1–0.3)</td>
<td>0.12 (0.06–0.24)</td>
<td></td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>1.37 (1.04–2.06)</td>
<td>0.33 (0.25–0.42)</td>
<td>0.18 (0.12–0.26)</td>
<td>0.02</td>
</tr>
<tr>
<td>III/IV</td>
<td>0.84 (0.69–1.21)</td>
<td>0.24 (0.17–0.33)</td>
<td>0.13 (0.08–0.21)</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1](https://www.eje-online.org)
large cohort studies published in the past decade (5, 7, 8, 22). This limitation reinforces the need to have a standardized pathological template that would contain key pathological features (e.g., Weiss score, Ki67%, resection margins) to facilitate a uniform interpretation and generalization of pathological data in ACC.

Figure 3 illustrates our current algorithm in approaching patients with localized ACC that combines the use of molecular markers (Ki67%) with other information such as resection margin and ENSAT stage for risk stratification and choosing adjuvant therapy.

The most common sites of distant metastasis in our study were the lungs and liver, followed by bone, in agreement with previous reports (43, 44, 45). Although it would have been useful to include the extent of the disease in the survival analysis, the imaging studies utilized (CT, MRI, PET scan and bone scan) at the time of diagnosis varied between patients during the study period. The lack of uniformity in the imaging studies may lead to a difference in the number of metastases identified and therefore could estimate inaccurately the burden of disease at diagnosis.

For patients with metastatic disease or unresectable tumors, the options are limited. Mitotane has been approved for ACC as an adjuvant therapy and for the treatment of advanced disease (46, 47). Moreover, the first randomized prospective study (ADIUVO trial, http://clinicaltrials.gov/ct2/show/study/NCT00777244) to assess efficacy of adjuvant mitotane in low-risk patients who underwent surgical resection is open for patient recruitment. In our study, mitotane was used in 71% of the patients, where almost 29% achieved therapeutic levels. We observed that the survival curves of the patients who achieved a mitotane level of 14 mg/l or higher showed early separation when compared with the patients with lower levels of mitotane. We believe this separation corresponds to the periods when most

Table 5 Multivariable Cox proportional hazards model for overall survival of patients with adrenocortical carcinoma.

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Hazard ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.0089 1.013 (1.003–1.024)</td>
</tr>
<tr>
<td>Functioning tumors vs nonfunctioning tumors</td>
<td>0.0196 1.400 (1.055–1.857)</td>
</tr>
<tr>
<td>Stage I/II vs III/IV</td>
<td>&lt;0.0001 0.438 (0.325–0.590)</td>
</tr>
</tbody>
</table>

Figure 2 Factors associated with the overall survival of patients with adrenocortical carcinoma. R0, no evidence of tumor; R1, macroscopically positive resection margins; R2, macroscopic residual disease; ENSAT, European Network for the Study of Adrenal Tumors; VTE, venous thromboembolism.

Figure 3 A suggested algorithm for the management of localized adrenocortical carcinoma. R0, no evidence of tumor; R1, macroscopic evidence of tumor; R2, macroscopic residual disease; RX, margins unknown. We recommend mitotane for 2–3 years.
patients would have been receiving mitotane and suggests a beneficial effect of reaching a therapeutic level of 14–20 mg/l, as shown repeatedly in the literature. Unfortunately, the retrospective nature of this review limited our ability to capture the mitotane dose, side-effect profile, or exact timing of therapy.

Currently used systemic therapies often combine mitotane with systemic agents. In the only completed phase III trial of ACC, the combination of etoposide, doxorubicin, and cisplatin with mitotane was superior to the combination of streptozocin with mitotane in terms of progression-free survival (5 vs 2.1 months); however, the two groups did not differ significantly in overall survival (24). In our cohort, cisplatin/etoposide and etoposide/doxorubicin/cisplatin regimens were the most common. In a previous study from our group, neither regimen conferred a significant advantage (48). Therefore, there is an urgent need for more efficacious treatment for this lethal disease. In fact, we have recently published our experience of dual inhibition of the IGF1 receptor and mTOR pathway, where stable disease was achieved for more than 6 months in 42% of the patients (49). Figure 4 illustrates our current management plan for patients with advanced/metastatic ACC.

The use of adjuvant radiotherapy in the context of ACC remains unclear. While some authors have proposed a decrease in local recurrences after adjuvant radiotherapy (48, 50), in a recent study published by our group that included the 16 patients who received adjuvant radiotherapy, we were unable to demonstrate improved survival, recurrence rate, or time to recurrence (29). Further prospective, multicenter studies are needed to better determine the impact of radiotherapy on recurrence and survival.

ACC in children is extremely rare, with an estimated incidence of 19 new cases per year in the United States (51). Carriers of TP53 mutations and some genetic syndromes are conditions that have been associated with ACC in children. In fact, it is estimated that about 50–80% of children with ACC carry a germline TP53 mutation (52, 53), making Li–Fraumeni syndrome the most common inherited condition in young patients with ACC. In our cohort, 12 patients (3.6%) were younger than 18 years old at the age of diagnosis, and 50% of the pediatric patients (six of 12) had Li–Fraumeni syndrome based upon clinical grounds or genetic testing.

Similar to older reports (25, 54), approximately one out of ten patients with nonhereditary ACC patients had other malignancies, with breast and prostate cancer being the most frequent ones. Despite this apparent risk for other malignancies, we only recommend age-appropriate cancer screening that is adjusted per personal and family history in the few patients who have long-term survival.

This study was limited by the inherent shortcomings of retrospective reviews and potential referral bias. Referral bias is likely more pronounced in rare diseases that require special expertise compared with more common illnesses that require well set standards of care and commonly available treatments (55). The main factors to cause this bias include the tendency to refer patients if they have unusual presentation, after failing prior treatments, and/or if they have advanced disease that requires special expertise. In ACC, referral bias is expected to result in worse outcome for the whole group if most inclusion subjects were referred after failing prior treatments.

Also, it is unknown how many patients are treated outside major centers and never referred for inclusion in such study design. Some of these patients may have been cured and did not require further treatment or they may have accepted their diagnosis as being terminal and chose to stay in their local communities (56). In our series, most of the patients had their initial surgical resection outside MDACC and then referred and it was often difficult to ascertain the cause of referral in all cases or the temporal relationship between recurrence and referral.

Nevertheless, the current study has multiple strengths including the summary of clinical experience with a large cohort of ACC patients treated at a single institution over the past decade, and description of our treatment approach in this rare disease.

The unchanged mortality observed over the decades in our cohort, which has also been described by a recent population study done in The Netherlands (8), underscores the urgency to find better treatments for ACC.
Conclusions

Despite better understanding of molecular pathways involved in ACC and the availability of new classes of anti-cancer therapy, the prognosis of ACC remains poor. Older age at diagnosis, functioning tumors, and incomplete resections are clinical factors associated with worse survival. Surgical expertise is important to achieve complete resections and to improve outcome. There is an urgent need for more efficacious systemic therapies to achieve complete resections and to improve outcome.

There is an urgent need for more efficacious systemic therapy, the prognosis of ACC remains poor. Surgical expertise is important to achieve complete resections and to improve outcome.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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